REMARKS

Accordingly, per the Office Action dated March 26, 2007, claims 66, 67, 87-94, 101, 133-136 were examined. Claims 66, 67, 87-94, 101, 133-136 were rejected.

In the instant Amendment and Response, accompanied by a Request for Continued Examination, Applicant has amended claims 66, 67, 94, 133, and 134. Applicant has canceled claim 101 in view of amendments to claim 66. Applicant has added new claims 137-141, which are drawn to the elected species. Support for the instant claim amendments and new claims are provided herein below. Applicant has made a number of significant amendments in order to clarify the difference in the instant invention over the teachings of '819. Support for the instant amendments can be found throughout the Specification, and most particularly in the following sections. For "nanocapsule", support may be found at Paragraph 34 for example. For "surfactant micelle", support may be found at Paragraph 74, for example. For "therapeutic effect", support may be found at Paragraph 48, for example. For "polypeptide, support may be found at Paragraph 52, as well as in the Examples, for example. For "precipitate comprising a polypeptide and cation precipitate", support may be found at Paragraphs 93 and 108, for example.

Before discussing the instant rejections, Applicant would like to take the time to generally discuss the instant invention and its distinguishing features over the prior art. It is respectfully pointed out the Examiner that Applicant lays claim to a very specific particle for which the inventor has been able to demonstrate unique and improved properties relative to prior art delivery vehicles. The Applicant has demonstrated that Applicant's particles deliver therapeutics to the **nucleus** of a targeted cell (such as a cancer cell), and **crucially**, avoid lysosomal degradation that has been recognized in the art as a major obstacle to new, important therapies (see, for example, Varga et al.: lysosomal degradation is "believed to be the greatest barrier for successful gene expression in non-viral delivery vehicles."[1])

It is emphasized to the Examiner that the prior art is very clear that the ordinary fate of non viral delivery vehicles upon internalization into the cell is fusion with a lysosome, leading to rapid degradation and clearance of the cargo. Consequently, for example, little or no cargo

[1] C.M. Varga, et al. "Receptor Mediated Targeting of Gene Delivery Vectors: Insights from Molecular Mechanisms for Improved Vehicle Design", *Biotechnology and Bioengineering*: 70(6) 593-605 (2000).

manages to enter the nucleus of a cell. The instantly taught particles avoid this fate due to their inventive properties, including their sub-50 nm size. Because of their ability to avoid lysosomal degradation, the instantly claimed particles have demonstrated disease clearance in a highly aggressive cancer model, without side effects, at remarkably low cumulative dosing.[2] Other disease indications in which remarkable efficacy has been demonstrated due to lack of lysosomal degradation include hemophilia A, where the particles effected a long term cure (>48 weeks) without initiation of Factor VIII antibodies in a transgenic mouse model.[3]

The nanocapsules can be described as a stabilized form of a normally transient species (a sub-50 nm micelle). The stabilization and small size is provided by a precipitated polypeptide (*via* precipitating cation) in an association with a surfactant micelle, which contains a surfactant and a bioactive component. The invention provides the first mechanically-stabilized sub-50 nm targeted nanocapsule with a bioactive component. In contrast, stabilization of prior art particles, such as liposomes, has been typically provided by incorporation of polyethylene glycol ("PEG"), a synthetic polymer that stabilizes due to its high molecular weight and hydrophilicity. Incorporation of PEG increases the size of liposomes, while the instant nanocapsules are of - smaller size, thus obtaining the benefits of efficient distribution and uptake afforded by smaller sized nanocapsules. The small size of the nanocapsules of the invention are achieved in part by combining stabilization and targeting properties in the same (precipitated) biocompatible polymer.

Claim 66 is directed to the inventive composition, i.e., targeted nanocapsules comprising a surfactant micelle core comprising a bioactive agent, and a surrounding shell comprising a polypeptide, wherein the peptide has been precipitated by a cation, useful for efficient intracellular delivery. As taught at paragraph 94 of the specification, the cation-precipitated shell solidifies, stabilizes, and reduces the size of the nanocapsule (to sub 50 nm sizes); the peptide providing multiple sites for a cation coordination of the precipitate. The Applicant's nanocapsules are thus significantly different from prior art relating to liposomes or to prior art relating to particles in which the shell is covalently linked to a surfactant containing core. Particle precipitates in the drug delivery art typically involve synthetic polymers (such as, for

[2] Unger G. et al., January 2007, Keystone Conference, "siRNA as Therapeutics", "Tumor Targeted delivery of siRNA using sub-50 nm nanocapsules"

[3] B.T. Kren et al. "Long-term Factor VIII Expression via *Sleeping Beauty* in Liver Sinusoidal Endothelial Cells of Transgenic Mice, *Molecular Therapy*, 15S1:952a, (2007)

example, PCPP). The Applicant respectfully submits that, as amended, Claim 66 is drawn to an important aspect of the present invention, as these nanocapsules have been demonstrated to have significant promise in improving therapies for serious human diseases.

New Claim 139 is similar to Claim 66 but additionally recites that the bioactive component is a polynucleotide in association with a nucleic acid condensing agent, the cation is Li^+, and that specific cellular uptake is *via* binding to a cell surface antigen or cell surface receptor *on a tumor cell*. Support for this amendment is found in the specification at, e.g., paragraphs 41, 124, and 168. This new claim focuses on another important aspect of the invention – polynucleotide-bearing nanocapsules useful in the treatment of cancer.

Applicant respectfully requests that the Examiner consider the above discussion as an aid to understanding the state of the prior art and the inventive contributions of the Applicant to the art of targeted non-viral delivery vehicles for bioactive agents. Applicant now turns to a discussion of the instant rejections, hereinbelow.

DOUBLE PATENTING

The Examiner has renewed the provisional rejection of claims 66, 67, 87, 88, 90, 92-94, 101, 133, and 134 and new claim 135 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 8 of copending Application no. 10/378,044.

The Examiner has also has renewed the provisional rejection of claims 66, 67, 87, 88, 90, 92-94, 101, 133, and 134 and new claim 135 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 13 of copending Application No. 10/958,999.

The Examiner has also rejected claims 66, 67, 87-94, 101, 133, and 134 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29 and 42 of U.S. Patent No. 6,632,671.

Application No. 10/378,044 has been abandoned and a continuation application, US 11/622,359, was filed January 11, 2007. The present application has an earlier priority date than the '044 and continuation application, and the Applicant respectfully requests that this rejection be withdrawn. Should the instant claims of the present application be allowed, and should the Office determine that the rejection should be maintained, the Applicant respectfully submits that the rejection should be made against the later filed continuation application.

The Examiner provisionally rejected claims 66, 87, 88, 90, 92-94, 101, 133 and 134, and rejected new claim 136, on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 10 and 13 of copending US Application Serial No. 10/958,999 (the "'099 application"). The present application has an earlier priority date than the '099 application, and the Applicant respectfully requests that this rejection be withdrawn. Should the instant claims of the present application be allowed, and should the Office determine that the rejection should be maintained, then the Applicant respectfully submits that the rejection should be made against the later filed '099 application.

The Examiner rejected claims 66, 67, 87-94, 101, 133 and 134, and rejected new claim 136, on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 29 and 42 of U.S. Patent No. 6,632,671. Final Rejection at page 3. Applicant acknowledges this rejection and will address this rejection once all other rejections have been resolved, or earlier.

CLAIM REJECTIONS UNDER 35 U.S.C. § 102(e)

The Examiner has renewed the rejection of claims 66, 67, 87, 88, 90-92, 94, and 101, and applies the rejection to new claim 135, as being anticipated by Unger, E.C. et al. (U.S. Patent No. 6,139,819), for the reasons of record set forth in the prior Office Action. The Examiner contends that (Office Action, page 5) "Unger et al. teach particles comprising a core provided by paramagnetic contrast agents, a surfactant molecule, such as cetyl alcohol, which is associated with a bioactive component, and a biocompatible polymer that coats the association between the bioactive component and the surfactant, wherein the biocompatible polymer provides specific cellular uptake." The Examiner also contends that Unger et al. teach that the particles have a size of about 30 nm, the particles can comprise a combination of two or more surfactants, a biocompatible oil, and a water miscible solvent. The Examiner contends that Unger et al. teach all of the limitations of the instant claims and accordingly the claimed invention is anticipated. The Examiner did not find Applicant's previously-submitted arguments in the Amendment dated 1/5/07 persuasive.

(a) Not all of the elements of the instant claims are taught by '819 (argued for Claims 138-141 only)

Applicant goes on record as disagreeing with the Examiner's rejection of claims 66, 67, 87, 88, 90-92, 94, and 101 and new claim 135 as being anticipated by Unger, E.C. et al. (U.S. Patent No. 6,139,819) and the Examiner's rationale for the rejection. However, in view of Applicant's earnest desire for an early allowance, Applicant, without prejudice, will not re-argue the rejection for these claims. Instead, Applicant respectfully directs the Examiner's attention to newly presented independent claim 139.

Applicant has made a number of significant amendments in order to clarify the difference in the instant invention over the teachings of '819. Support for the instant amendments can be found throughout the Specification, particularly as noted previously above.

Claim 139 contains the following limitations:

A. a *surfactant micelle comprising a core provided by a bioactive component, which is a polynucleotide and has a therapeutic effect, and a surfactant having an HLB value of less than about 6.0 units*,

B. *a shell surrounding the surfactant micelle, said shell comprising a precipitate comprising a polypeptide and a cationic precipitating agent comprising* Li^+,

C. *wherein the polypeptide provides specific cellular uptake by binding to a cell surface antigen or cell surface receptor on a tumor cell,*

D. *subject to the limitation that the nanocapsules have an average diameter of less than about 50 nanometers as measured by atomic force microscopy following drying of the particles.*

The Examiner is requested to note key limitations. The phrase "biocompatible polymer" has now been replaced by "polypeptide". The phrase "shell" has been further modified with the limitation that the shell comprises a precipitate of the polypeptide and a cationic precipitating agent comprising Li^+. Furthermore, the term "provides specific cellular uptake" has been further limited to "by binding to a cell surface antigen or cell surface receptor on a tumor cell". The bioactive component is limited to a polynucleotide that is directed to a tumor cell. Support for the instant amendments include the Specification at Paragraph 92 and Example 1A, page 53 (for polynucleotide) and page 168 (for tumor targeting)

As taught in Paragraph 94 of the specification, the cation-precipitated shell solidifies and reduces the size of the nanocapsule; an iontophoretic polymer (such as the claimed polypeptide) provides multiple sites for a cation coordination of the precipitate. It is respectfully submitted that the particles taught by '819 in particular do not include a cation-precipitated shell comprising

a polypeptide and a cation comprising Li^+. This amendment in particular distinguishes from '819, and other prior art. The Applicant submits that the prior art typically teaches stabilization as being derived from either a covalent association of a bioactive component and other components, or incorporation of polyethylene glycol (PEG), which stabilizes due to its high molecular weight and hydrophilicity. PEG methods in particular result in larger size liposomes than the instantly claimed particles, which are specifically limited to sub 50 nm particles.

With respect to the claimed limitation of Li^+, Applicant notes that while '819 teaches lithium carbonate at Col. 24, lines 42-56, '819 does not teach that lithium is a precipitating agent and it is not taught that the shell comprises a precipitate of lithium and a polypeptide. Instead, lithium carbonate is taught merely as a generic salt for a "gaseous precursor material derived from a salt"; such a lithium carbonate or bicarbonate. '819 also teaches a chemical reducing agent, lithium aluminum hydride or lithium aluminum diisobutyl hydride,('819, Col. 48, lines 43 to Col. 49, line 8) to produce covalent Schiff's base linkages. It is respectfully submitted that '819 does not teach the element of lithium as a precipitating agent and a shell comprising a precipitate of lithium and a polypeptide.

It is respectfully submitted that '819 does not teach all of the elements of the instant claims 138 (wherein cation is Li^+) , and 139-141, as currently amended. Reconsideration is respectfully requested.

(b) 819 is not a proper anticipatory reference under In re Arkley *and its progeny*

Should the Examiner disagree with the Applicant's assertion that not all the elements of the instant claims are present in '819, as is discussed above, it is respectfully submitted that even if, *arguendo,* all "elements" are disclosed in the reference, the disclosure of '819 still does not rise to the level of an anticipatory reference. Specifically, the legal standards for a proper anticipatory reference have not been met by '819, for reasons explained in more detail below. This argument is presented for claims 66, 67, 87, 88, 90-92, 94, 101, 135, and new claims 137-141.

Applicant notes that for an anticipation rejection, the reference must clearly and unequivocally disclose the claimed compound without any need for "picking" or "choosing" from among the disclosures in the reference. *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). In this case, the Court of Appeals held that "rejections under 35 USC 102 are proper only when the

claimed subject matter is identically disclosed or described in 'the prior art.'. . . [and the cited] reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." The *Arkley* Court held that the portions of the reference relied upon by the Patent Office did not identically describe the claimed subject matter and thus the rejection was invalid. *Id.* at 588. The *Arkley* claim was directed to a particular cephalosporin which could be synthesized by a particular tertiary amine; this tertiary amine was "mentioned elsewhere" as an example of how cephalosporin C may be converted to different types. *Id.* However, the court held that "there is nothing in the teachings relied upon by the Patent Office which 'clearly and unequivocally' directs those skilled in the art to make this selection nor any indication that [the reference] ever made the selection". *Id.* The Court specifically said that the reference "point[ed] to no particular one of the myriads of compounds, actual and potential, containing the cephalosporin C(A) nucleus." *Id.*

Numerous published Board decisions have relied on *In re Arkley* for overturning Examiners' anticipation rejections in light of the prohibition against "picking and choosing", or where the claimed invention was not "identically disclosed in the prior art."[4] An example of a recent Board decision is *Ex parte Goldberg*, 2002 Pat. App. LEXIS 207. The claim was directed to administering human mesenchymal cells having a fibroblastic morphology for repairing cartilage. The Board stated: "the examiner has made very specific selections from the genus of options set forth in [the reference]. In our opinion, this picking and choosing is not sufficient to establish a prima facie case of anticipation. When the claimed invention is not identically disclosed in a reference, and instead requires picking and choosing among a number of different options disclosed by the reference, then the reference does not anticipate." *Id.*, citing *Akzo N.V. v. International Trade Commission*, 808 F.2d 1471, 1480, (Fed. Cir. 1986); *In re Arkley,* 455 F.2d 586, 587-88, (CCPA 1972).

[4] See, e.g., *Idacon v. Central Forest Products, Inc.*, 3 U.S.P.Q.2D (BNA) 1079, (Okl. 1986) ("[A]n anticipation must speak affirmatively and with certainty; must disclose the invention without debate; it is not enough that the proper proportion . . . might empirically be hit upon"); *see also, e.g., Ex Parte Moody*, 2004 Pat. App. LEXIS 137; *Ex Parte Levy*, 1990 Pat. App. LEXIS 18; 17 U.S.P.Q.2D (BNA) 1461; *Ex Parte Schmidt*, 2001 Pat. App. LEXIS 91; *In re Marshall,* 578 F.2d 301; (CCPA 1978); *Ex Parte Goldberg*, 2002 Pat. App. LEXIS 207.

Applicant respectfully submits that under the standard of *In re Arkley* and its progeny, '819 **fails** as a proper anticipatory reference. The Examiner has impermissibly "picked" and "chosen" various disclosures throughout the extremely lengthy '819 patent and the claimed invention "is not identically disclosed" in '819 **as is legally required** for an anticipation rejection.

Applicant first notes that '819 is extremely lengthy at 132 columns, with almost dictionary-type disclosure. '819 teaches **contrast agents for diagnostic and therapeutic use in conjunction with ultrasound**. See Abstract. In contrast, the present invention is directed to a nanometer-scale, cell-targeted delivery vehicle, containing a therapeutic bioactive agent associated with hydrophobic surfactant, surrounded by a cationic-precipitated polypeptide, useful for efficient intracellular delivery. The Examiner has relied on disparate sections of '819 and relied on picking and choosing among a number of different options disclosed by the reference, to conclude that the '819 patent teaches the presently claimed invention. Applicant respectfully submits that the Examiner has misapplied '819, as discussed below with more specificity.

With respect to Applicant's limitation to a surfactant having an HLB value of less than 6 units; the Examiner in the Office Action dated June 14, 2006 points to Col. 18, line 61. Applicant notes that this section of '819 teaches perhaps 120 different lipids, in the section starting Col. 17 and continuing to Col. 21. A review of these lipids reveals that the majority of the lipids, including those taught as preferred lipids in '819 (Col. 17, lines 23-29; Col. 21, lines 64-67), are hydrophilic lipids, in contrast to Applicant's lipids (surfactants) which are limited to those that are quite hydrophobic. Applicant submits that this is hardly an "identical" disclosure, that '819 does not direct one skilled in the art to narrow '819's list to hydrophobic lipids, as required by the instant claims, and selection of a surfactant having an HLB value of less than 6 units certainly requires picking and choosing from '819's list.

With respect to the limitation taught by the Applicant of the polypeptide for the shell, Applicant notes that a "polymer" as a stabilizing compound is taught by '819 to include any number of materials, including polysaccharides, cellulosic polymers, polyethylenes, polypropylenes, polyurethanes, polyvinyl chlorides, nylon, polystyrene, synthetic polymers such as polymers of acrylic acid, siloxanes, ethylene glycol, polyethylene glycol, and so forth (Col. 31 line 1 to line 43.) Again, Applicant submits that this is hardly an "identical" disclosure, that '819 does not teach one skilled in the art to choose a polypeptide (which is capable of iontophoretic

exchange), as required by the instant claims, and selection of a polypeptide requires picking and choosing from '819's list.

With respect to the limitation taught by the Applicant of a size of less than 50 nanometers, the Examiner points to Col. 28, lines 51-53. The disclosed size range of '819's vesicles are between 30 nanometers and about 100 micrometers. The range taught by '819 is exceedingly broad, or greater than 3000 fold. In contrast, Applicant's range of less than 50 nm overlaps by less than 20 nm, or less than 2 fold. Applicant has therefore chosen approximately 0.15% of the range claimed by '819 for an appropriate size range of their particles. The '819 patent's large range does not have the requisite specificity to anticipate or suggest the instant claims to nanocapsules of less than 50 nm average size containing a therapeutic agent in a micelle core surrounded and in association with a polypeptide-cation precipitated shell. Conversely, the only reference to particles of 30 nm in the '819 patent is at the aforementioned col. 28, line 52, and that is in combination with particles of 100 um size. This generic teaching hardly suggests, much less anticipates the nanocapsules of the instant claims. The '819 patent also refers to particles of "less than 100 nm" for possible applications in cancer (col. 63, lines 24-25); this teaching neither anticipates nor suggests nanocapsules that must be, on average, less than half this size. Most tellingly, the smallest particle in the examples of the '819 patent is 200 nm (see Example 39A), and this is a *prophetic* example. Finally, the only other reference in the '819 patent to particles of small size is at col. 68, lines 24-35, where reference is made to "an emulsion containing droplets with a diameter of 54 nm", and that "an emulsion of this particular size could be easily achieved by the use of an appropriately sized filter." This "nanodrop" appears to be only the droplet portion of the particle, and thus the size refers to the droplet, and not the emulsion in which it might be contained; thus, the ultimate particle would be larger than the nanodrop, which is already larger than the average size of the nanocapsules of the instant claims. Applicant submits that this is hardly an "identical" disclosure, and selection of less than 50 nm requires selecting a vanishingly small subset of '819's range.

With respect to the limitation taught by Applicant that the shell includes a "precipitate comprising a polypeptide and a cationic precipitating agent, wherein the polypeptide", Applicant submits that cationic precipitation of a polypeptide species resulting in a sub 50 nm particle is not taught in '819. The only teaching in '819 even slightly related to this concept is in Example 11, a **prophetic** example, which teaches that "PCPP [a synthetic polymer] will be crosslinked by

the divalent calcium ions to produce a relatively homogeneous population of spherical gel vesicles." Applicant notes that the particles taught in Example 11 of '819 contain a hydrophilic surfactant (in contrast to claimed hydrophobic surfactants), a synthetic polymer (in contrast to the claimed polypeptide), a gas cargo (in contrast to the claimed therapeutic component), and a diameter of 3-15 μm[5] (in contrast to the claimed size range of less than 50 nm). Even though '819 does not recite the presumed size of the precipitated particle, it is clear that sub-50 nm particles could not be achieved by this prophetic example due to, for example, the presence of PEG, a high molecular weight species. Again, Applicant submits that this is hardly an "identical" disclosure, and still less even rises to the level of a "teaching".

Applicant also notes that for an anticipation rejection, the elements of the reference must be arranged as required by the claim. *In re Bond*, 910 F.2d 831, (Fed.Cir. 1990). Applicant respectfully submits that nowhere in '819 is there disclosed the elements as required by the claim, i.e., a therapeutic bioactive component associated with a hydrophobic surfactant and surrounded by a polypeptide shell precipitated with a cation and useful for receptor-based targeting of cells, in a nanocapsule of less than about 50 nanometers in diameter.

In summary, Applicant respectfully submits that the Examiner misapplies '819 as an anticipatory reference in the instant case. '819 does not 'clearly and unequivocally' direct those skilled in the art to make the claimed invention, nor is there any indication that [the reference] ever made the selection, as required by *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). The Examiner has not complied with the Board's statement that anticipation does not occur "[w]hen the claimed invention is not identically disclosed in a reference, and instead requires picking and choosing among a number of different options disclosed by the reference." *Ex parte Goldberg* (2002 Pat. App. LEXIS 207), as discussed above. In light of this analysis of the disclosures of '819 as compared to the instant invention, as disclosed and claimed, Applicant respectfully requests withdrawal of this rejection.

(c) Applicant argues that the range is not taught with "sufficient specificity"

Applicant has previously made this argument in the Response dated 1/5/07. The Examiner acknowledged a "sufficient specificity" argument in Office Action on page 4, but

[5] Applicant notes that Example 11 is copied substantially from USPN 5,487,390, Langer et al., Example 2, although '819 omits the stated resultant particle size of 3-15 microns.

appears not to have recognized the argument that Applicant was making. Examiner appears to conflate the "sufficient specificity" argument (occurring at pages 14-16 of the 1/5/07 Response) with Applicant's later occurring and unrelated non-enablement argument (occurring at pages 16-20 of the 1/5/07 Response). The Examiner does not appear to have responded to the "sufficient specificity" argument in view of the Examiner's apparent confusion.

The "sufficient specificity" argument focuses on MPEP § 2131.03(II) relating to disclosure of ranges. Here, the MPEP directs Examiners to be alert to the fact that where prior disclosure of a range merely "touches" or "overlaps" the prior art range, the prior art may **not** anticipate the claimed range, in view of a recently decided case (*Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006)). The Examiner is respectfully requested to review the referenced MPEP section prior to reviewing Applicant's argument below.

For the Examiner's convenience, Applicant's argument related to this issue is briefly re-presented herein. The MPEP notes at § 2131.03(II) that "[w]hen the prior art discloses a range which touches or overlaps the claimed range, **but no specific examples falling within the claimed range are disclosed**, a case by case determination must be made as to anticipation. (emphasis added)" Applicant notes that in '819, the disclosed size range is between 30 nanometers and about 100 micrometers, apparently overlapping Applicant's claimed range of an average diameter of less than about 50 nanometers. **Applicant, however, upon careful review of the Examples section of '819 submits that none of the examples in '819 disclose a vesicle of less than about 200 nanometers.** Accordingly, the instant situation falls squarely within the scope of this section of the MPEP, necessitating that the Examiner undertake a determination as to anticipation specific to this particular case.

The MPEP then continues (at § 2131.03(II)), "[i]n order to anticipate the claims, the claimed subject matter must be disclosed in the reference with 'sufficient specificity to constitute an anticipation under the statute.' What constitutes a 'sufficient specificity' is fact-dependent. If the claims are directed to a narrow range, and the reference teaches a broad range, . . . it may be reasonable to conclude that the narrow range is not disclosed with 'specific specificity' to constitute an anticipation of the claim," *citing Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Again, this case falls squarely within the confines of the *Atofina* case and this section of the MPEP. The disclosed size range of '819's vesicles are between 30 nanometers and about 100 micrometers. The range taught by '819 is thus between 30 nm and

100 micrometers and is exceedingly broad. The two ends of the '819 range are different by three to four orders of magnitude or greater than 3000-fold.

In contrast, the instant application's claim 66 states that Applicant's particles have an average diameter of less than about 50 nanometers. Applicant's claimed range (i.e., less than 50 nm) overlaps only about 20 nm, at most, out of '819's disclosed range of approximately 100,000 nm, fitting the instant case squarely within the confines of the *Atofina* case. In fact, in *Atofina*, the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 350-450 degrees C with sufficient specificity to be anticipatory. *Id.* at 1000. It can clearly be seen that the ranges disclosed in the instant claims and in '819 overlap far less than the ranges in *Atofina,* further supporting Applicant's argument that the Federal Circuit's finding of no anticipation in *Atofina* is applicable in this case.

Reconsideration of the anticipation rejection in light of MPEP § 2131.03(II) and *Atofina* is respectfully requested.

(e) Applicant's response to Examiner's comments on why previous rejections are maintained

On pages 5-6 of the Office Action, the Examiner disagreed with Applicant's clarifying that the term "encapsulated" was not used in '819 for bioactive materials, merely for gas. Applicant did not argue this point for any of the claims; it was merely included to correct a mis-quotation of '819. Nevertheless, Applicant does not re-raise this point.

On pages 6-7 of the Office Action, the Examiner found the Declaration ineffective for showing nonenablement of '819 towards the instantly claimed invention. Applicant states for the record disagreement with the Examiner's conclusion as to enablement, and herein retains the right to re-present this argument at a later date. However, in view of the amendments to the claims and the other arguments presented herein, Applicant does not re-present this argument. Applicant submits that the claims, as amended, distinguish the nanocapsules of the invention from the vesicles broadly described in the '819 patent.

On pages 7-8 of the Office Action, the Examiner states that the term "monolayer" was not present in claims 66, 67, 87-94, 101, 133, 134, and 136. Applicant notes that they only argued the term "monolayer" for claim 135, not for the other claims as contended by the Examiner. Please see Response, 1/5/07, at page 20. Although Applicant disputes the Examiner's conclusion

that due to '819's redefinition of the term vesicles, the term vesicle as used by '819 defines "a genus of vehicles would necessarily include monolayer micelles." However, in view of the amendments to the claims and the other arguments presented herein, Applicant does not re-present this argument. Applicant submits that the claims, as amended, distinguish the nanocapsules of the invention from the vesicles broadly described in the '819 patent.

> On page 7 of the Office Action, the Examiner states that:
>
> [t]he instant specification clearly discloses that the use of a surfactant with a HLB value about 5.0 units (such as cetyl alcohol) results in particles of about 50 nm (p.5, paragraph 63, claims 1 and 90). Since Unger et al teach that cetyl alcohol can be used to prepare their particles, these particles must have a diameter of 50 nm or less, absent evidence to the contrary.

Office Action at page 7. While the Applicant respectfully submits that the Examiner has misconstrued the teachings of the instant application (paragraph 63), which states that use of surfactants with HLB values less than 6 or 5 "facilitate preparation of nanocapsules having a diameter of less than about 50 nm" (not "**must** have a diameter of 50 nm or less", as Examiner contends), the amendments to the claims herein moot the argument.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

The Examiner rejected claims 66, 67, 87-94, 101, 133, and 134 under 35 U.S.C. § 103(a) as having been obvious over the '819 patent in view of Schneider *et al.*, FEBS Letters, 1998, 429:269-273 (hereinafter "Schneider"). Final Rejection at page 8. The Examiner cites Schneider et al. for the teaching that polypeptides derived from the C-terminus of tenascin are capable of mediating specific gene delivery to cells expressing receptors for tenascin, and '819 for teaching particle coated with a biocompatible polymer that provides a targeting ligand for specific cellular uptake. The Examiner concludes that one of skill in the art would have known and would have been motivated to modify the particles of Unger et al. by using the polypeptides of Schneider et al.

According to MPEP § 2142, "[i]n order to establish a prima facie case of obviousness, three basic criteria must be met. First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second there must be reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations," *citing In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

In addition, under 35 U.S.C. § 103, each claim must be considered as a whole. As stated by the Federal Circuit in *In re Wright*, 838 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988), "[i]t is the invention as a whole that must be considered in obviousness determinations. The invention as a whole embraces the structure, its properties, and the problem it solves." Similarly, "[i]n determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety." *Rockwell International Corp. v. United States*, 47 USPQ2d 1027, 1031 (Fed. Cir. 1998).

'819 is primarily directed to **contrast agents for diagnostic and therapeutic use in conjunction with ultrasound**. See Abstract. In contrast, the present invention is directed to a nanometer-scale, cell-targeted delivery vehicle containing a therapeutic agent associated hydrophobic surfactant, surrounded by a cationic-precipitated polymer, for efficient intracellular delivery. In view of the teachings of this art, Applicant respectfully submits that there is no motivation to combine the teachings to arrive at the instantly claimed invention, and further, there is not a reasonable expectation of success.

MPEP 2143.01(I) requires that for a proper *prima facie* case of obviousness, the references cited must suggest the desirability of the claimed combination. However, Applicant respectfully submits that '819 and Schneider et al. do not teach the desirability of the claimed invention. The disclosures of '819 are directed primarily to contrast agents for diagnostic and therapeutic use in conjunction with ultrasound, with the contrast agents being primarily gaseous bubbles. With respect to teachings of '819 of delivery of therapeutic agents, '819 (in only one portion, reproduced below) teaches that release of the therapeutics is achieved **via application of ultrasound**:

> [C]ompositions of the present invention, particularly vesicle compositions, may be employed to administer bioactive agents, including therapeutic materials. Thus, for example, in the case of patients suffering from [atrial fibrillation], the present methods and compositions may be employed not only to diagnose the presence of coagula, but also or instead to target the coagula with a bioactive agent, such as a pharmaceutical agent, including an anticoagulant. As discussed more fully hereinafter, the anticoagulant (or additional or other **bioactive agent**) **may be released at the desired site, such as at the site of the coagulum, by the appropriate application of ultrasound which, in the case of vesicle compositions, may cause rupture of the vesicles and release of the entrapped anticoagulant.** Thus, focused treatment of coagula with anticoagulant

medication may be achieved with the methods and compositions of the present invention, such focused treatment being unavailable heretofore. (Col. 16, lines 18-42)

Therefore '819 broadly teaches a particle comprising a bioactive agent that requires ultrasound for its release. With specific respect to use of precipitated particles, '819 teaches a particle that comprises gas. See Example 11 (the only teaching of precipitated particles in '819). Example 11 does not disclose a method for use of the gas-filled precipitated particles. However, based on the art, it can be reasonably stated that said particles are not intended to release the contents, but rather to deliver the contents, intact and **unreleased**, to an **extracellular** location where they can be imaged.

In contrast, the instantly claimed particles provide release for **intracellular** delivery of a therapeutic bioactive agent **without** application of ultrasound energy. Accordingly, '819 **does not at all suggest the desirability of the present invention**. Thus, one skilled in the art would not have been motivated to utilize the teachings of '819 and Schneider, et al. in solving Applicant's problem, i.e., delivery of bioactive agents to the interior of a cell while avoiding fusion with lysosomes.

The lack of any teaching in '819 or Schneider et al. suggesting the desirability of the combination is further evidenced by the fact the Examiner had to reach deeply into the vast disclosure of '819 and rely on disparate sections of '819 and picking and choosing among a large number of different options disclosed by the reference. For example, the disclosed size range of '819's vesicles is between 30 nanometers and about 100,000 nanometers. In contrast, Applicant's range of less than 50 nm overlaps by less than 20 nm, or less than 2 fold. Applicant has therefore chosen approximately 0.15% of the range claimed by '819 for an appropriate size range of their particles. '819 also teaches perhaps 120 different lipids, in the section starting Col. 17 and continuing to Col. 21. A review of these lipids reveals that the majority, including those taught as preferred lipids in '819, are hydrophilic lipids, in contrast to Applicant's lipids which limited to those that are quite hydrophobic. Additionally, with respect to the limitation taught by the Applicant of the polypeptide for the shell, Applicant notes that a "polymer" is taught by '819 to include any number of materials, including polysaccharides, cellulosic polymers, polyethylenes, polypropylenes, polyurethanes, polyvinyl chlorides, nylon, polystyrene, synthetic polymers such as polymers of acrylic acid, siloxanes, ethylene glycol, polyethylene glycol, and so forth (Col. 31 line 1 to line 43.)

The Schneider et al. disclosure does not make up for the deficiency of '819. Schneider et al.s' teaching of using polypeptides derived from the C-terminus of tenascin for mediating specific gene delivery to cells expressing receptors for tenascin. Putting Schneider et al.'s tenascin coat on the therapeutic agent-containing vesicles as taught by '819 (which teaches release of the therapeutic agent by ultrasound to the extracellular space) would not lead the skilled person to arrive at the instantly claimed invention.

Accordingly, it is respectfully submitted that a proper case for combining the references, as required by MPEP 2143.01(I) has not been made out because the cited references do not suggest the desirability of the claimed combination. Reconsideration is respectfully requested.

Another requirement for a *prima facie* case of obviousness is that the proposed modification "cannot render the prior art unsatisfactory for its intended purpose." MPEP 2143.01(V). If the claimed combination renders '819 (or Schneider et al.) unsatisfactory for their intended purposes, then legally there is no suggestion or motivation to make Applicant's claimed modification. Applicant references Applicant's above discussion regarding the lack of suggestion of the desirability of the combination, and also points out that Applicant's modifications render '819 (and Schneider et al.) unsatisfactory for their intended purposes. '819 teaches a vesicle comprising a bioactive agent with ultrasound energy used for its release. However, it is known in the art that increasing the rigidity of a particle (i.e., by cationic precipitation of a polypeptide shell) and decreasing the size of the particle (i.e., to sub 50 nm sizes) would render such modified particles **less susceptible** to destruction *via* ultrasound energy. Such particles would require higher levels of ultrasound energy for release, which is undesirable because higher levels of ultrasound energy increase the risk of damage to the patient's tissue. Accordingly, Applicant's claimed modifications to the teachings of '819 would render '819's vesicles unsatisfactory for its intended purpose, i.e., delivery via ultrasound. The Schneider et al. disclosure does not make up for the deficiency of '819. Putting Schneider et al.'s tenascin coat on the therapeutic agent-containing vesicles as taught by '819 (which teaches release of the therapeutic agent by ultrasound to the extracellular space) would not obviate the unsatisfactory nature of Applicant's claimed particles for the purposes of '819. Accordingly, it is respectfully submitted that a proper case for combining the references, as required by MPEP 2143.01(V) has not been made out because the instantly claimed modifications render '819 unsatisfactory for its intended purpose, i.e., release of a therapeutic agent by ultrasound to the extracellular space.

Applicant respectfully submits that in light of the above arguments, the Examiner has not demonstrated a *prima facie* case of obviousness. Reconsideration is respectfully requested.

In the Office Action, the Examiner argued that "testing different surfactants for their capacity to render particles of desired size and activity is routine experimentation" (Office Action page 11) and argues that a reasonable expectation of success is provided. Examiner argues that "it is noted that the particles of '819 must have the same qualities (i.e., taken up by caveolae) because they have the same size." Applicant strongly disagrees with the Examiner's statement, because it is contrary to the teachings in the art. **Specifically, it is known in the art that the greatest impediment to successful gene expression via non-viral delivery vehicles is lysosomal degradation:** "[r]egardless of the targeting ligand employed, receptor-mediated internalization results in the sorting of complexes toward lysosomal degradation . . . Endosomal sorting toward the lysosomal degradation fate is thus believed to be the greatest barrier for successful gene expression via non-viral delivery vehicles." CM Varga et al., "Receptor Mediated Targeting of Gene Delivery Vectors: Insights from Molecular Mechanisms for Improved Vehicle Design, Biotechnology and Bioengineering: 70(6) 593-605 (2000). Other non-viral vectors, made by standard methods in the art and being of micron size range, have been conclusively shown to be trafficked to lysosomes intracellularly.[6] **Therefore, the art teaches that the standard fate for the typical delivery vehicle is lysosomal degradation**. It is noted that '819 provides **no** Examples of manufactured vesicles of size of less than 50 nm, and in view of the teachings of lysosomal degradation troubling the vesicles of the prior art, '819 provides no teaching of avoidance of the lysosomal fate for the '819 vesicles.

Thus, Applicant's success in achieving avoidance of lysosomal degradation could not be predicted based on the teachings of '819. Applicant therefore submits that success in producing stabilized particles of sub-50 nm size that avoid lysosomal degradation is not a routine achievement in the art, rather, it is a significant leap over the teachings of the prior art, and as such, is an unexpected success. Accordingly, Applicant's particles, which avoid the lysosomal degradation which reduce the effectiveness of non-viral delivery vehicles, provide significant and unexpected results over conventional particles.

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[6] *See, e.g.*, Colin, M. et al. "Cell delivery, intracellular trafficking and expression of an integrin-mediated gene transfer vector in tracheal epithelial cells", (2000) *Gene Therapy* 7:139-152; Colin, M. et al. "The nuclear pore complex is involved in nuclear transfer of plasmid DNA condensed with an oligolysine-RGD peptide containing

Reconsideration is respectfully requested.

Claims 66, 67, 87, 88, 90-92, 94, 101, 135, and 136 are rejected under 35 U.S.C. 103(a) as being anticipated by Unger, E.C. et al (US Patent No. 6,139,819), in view of both Medina (U.S. Patent No. 5,650,543) and Quay (U.S. Patent No. 5,707,606) (Final Rejection at page 12). The rejection is made for the following reasons.

In response to Applicant's argument that the '819 patent do not teach acetylenic diols, Examiner states

> Medina teaches ethoxylated acetylenic diols as excellent surfactants because of their ability to reduce surface tension. Medina does not teach using their surfactant for the fabrication of nanoparticles. However, Quay teaches the use of acetylenic diols or blends thereof for the preparation of stable and biocompatible colloidal dispersions use for enhancing the contrast in an ultrasound image.

(Final Rejection at page 12, citations omitted.) Examiner states it therefore

> would have been obvious to modify the particles of the Unger et al by using acetylated diols, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Medina clearly teaches that such surfactants are able to decrease the surface tension.

(Final Rejection at page 13.)

Applicant incorporates by reference into this paragraphApplicant's arguments regarding the deficiencies of the teachings of '819, in that '819 fails to suggest the desirability of the claimed combination. Not only that, but Applicant's claimed modifications render the prior art unsatisfactory for its intended purpose. Further application of Quay and Medina fail to make up for the deficiencies of the teachings of '819.

Medina teaches surface tension-modifying capacities of ethoxylated acetylenic diols. Applicant submits that Medina does not distinguish the ethoxylated acetylenic diols by hydrophobic or hydrophilic properties. It is known in the art that ethoxylated acetylenic diols can have HLB values ranging from about 4 or less to about 17 or higher, dependent in part upon the concentration of ethoxyl. Quay merely teaches ethoxylated acetylenic diols for colloidal dispersions for enhancing contrast. Further, Quay discloses reducing surface tension does not necessarily result in smaller particle size. See Example 5. Sodium perfluorooctonoate was added to a particle formulation "to stabilize the formulation because this addition reduces

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nuclear localization properties" (2001) *Gene Therapy* 8:1643-1653 (Both included with an IDS co-submitted with this paper).

interfacial tension". However, Quay observed particle size increased significantly (from about 150 nm to about 1,060 nm) after the addition of sodium perfluorooctonoate.

Accordingly, neither Quay nor Medina suggest the desirability of the claimed combination, nor do they obviate the unsatisfactory nature of Applicant's claimed particles for the purposes of '819. Accordingly, it is respectfully submitted that a proper case for combining the references, as required by MPEP 2143.01(V) has not been made out because the instantly claimed modifications as allegedly taught by Quay or Medina render '819 unsatisfactory for its intended purpose, i.e., release of a therapeutic agent by ultrasound to the extracellular space.

Reconsideration is respectfully requested.

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

Date: September 26, 2007

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